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Episodes of severe hypoglycemia is associated with a progressive increase in hemoglobin A1c in children and adolescents with type 1 diabetes

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Abstract:

Objectives: To investigate the trajectory in glycemic control following episodes of severe hypoglycemia (SH) among children and adolescents with type 1 diabetes (T1D).

Methods: A Danish national population-based study comprising data from 2008-17. SH was defined according to the 2014 ISPAD guidelines. A mixed model was applied with HbA1c as outcome and SH episodes and time since first episode as explanatory variables. Data were adjusted for age, gender and diabetes duration.

Results: A total of 4,244 children (51.6% boys) with 18,793 annual outpatient visits were included. Mean (SD) age at diabetes onset was 9.0 (4.1) years. Median diabetes duration at inclusion in the study was 1.2 (Q1=0.9, Q3=3.0) years, and median diabetes duration at last visit was 5.0 (Q1=2.7, Q3=8.1) years. A total of 506 children experienced at least one episode of SH during the nine-year follow-up; 294 children experienced one episode, 115 two episodes and 97 three or more episodes of SH.
HbA1c increased with episodes of SH and in the years following the first episode. The glycemic trajectory peaked 2-3 years after an SH episode. The accumulated deterioration in glycemic control was in the range of 5% in patients with two or more episodes equivalent to an increase in HbA1c of 4 mmol/mol (HbA1c ~ 0,4%).

Conclusion: Severe hypoglycemia was followed by a progressive and lasting increase in HbA1c among Danish children and adolescents with T1D. Thus, in addition to the known risk of new episodes of hypoglycemia and cognitive impairment, SH contributes to long-term diabetes complications.

Key words: Diabetes, children, adolescents, severe hypoglycemia, HbA1c

Introduction

Target hemoglobin A1c (HbA1c) for glycemic control in children and adolescents with type 1 diabetes (T1D) is the lowest achievable HbA1c without undue exposure to severe hypoglycemia (SH) as well as a balanced approach considering quality of life and burden of care[1].

The Diabetes Control and Complications Trial (DCCT) showed that an improvement in glycemic control was achieved at the expense of an increase in SH[2]. However, improved glycemic control has become a minor risk factor for SH. Thus, the frequency of SH decreased in the period 2004-2012 compared with the period 1995-2003, which paralleled increasing use of modern diabetes technology such as insulin analogs, insulin pumps and glucose sensors[3].

Recently, two comprehensive international studies in children and adolescents with T1D from the population-based German/Austrian registry and the U.S. in the period 2011-12[4], and from the Scandinavian countries in the period 2008-12, respectively[5], did not find any association between HbA1c and SH.

Though the risk of SH is decreasing, it is still a rather frequent acute complication. Data from the Danish Childhood Diabetes Database (DanDiabKids) showed an incidence of 7.6 per 100 person-years in children below the age of 17 in the period 2008-2013[6]. This is in agreement with results in a Scandinavian study comprising children and adolescents reporting an SH incidence of 6.0 per 100 person-years in the period 2008-12[5]. Although the risk of SH is decreasing and not specifically associated to low HbA1c, children with fear of hypoglycemia often have elevated HbA1c and many caregivers still connect SH with low HbA1c and prefer a less tight metabolic control. Fear of hypoglycemia is thus a major psychological burden for patients and families in the pediatric/adolescent setting [7,8]. In some families, fear of hypoglycemia becomes a barrier in the everyday life for children and adolescents. Due to the glucose-lowering effect of physical activity, participation in social events and sports may be avoided potentially impacting on quality of life and perception of increased disease burden[9].

One or more episodes of SH may have implications on lifestyle and/or diabetes-regulatory behavior potentially impacting on glycemic control and risk of long-term diabetes complications. The aim of this study was to describe the trajectory in HbA1c after episodes of SH among children and adolescents with T1D registered in the DanDiabKids.

Methods

Data collection

Data were collected as previously described[6] with yearly registrations in the DanDiabKids from diabetes onset until the age of 18[10]. All Danish children and adolescents with newly diagnosed T1D according to the WHO criteria[11] were included in the DanDiabKids. The register has a data completeness concerning incident cases of 99 %[10] and includes data on age, gender, ethnicity, diabetes duration, self-monitored blood glucose (SMBG), treatment modality (insulin pen/pump),

insulin type, HbA1c (IFCC) and anthropometric measures. Completeness of annual registrations of SH is > 90% in the register[12].

Study population

In the period 2008-17, the DanDiabKids comprised a total of 5,538 children and adolescents below 18 years of age. All participants with T1D and diabetes duration exceeding six months were included in the study. Participants with missing data for SH and/or HbA1c for a period of more than 18 months were excluded from subsequent analysis, resulting in analysis of 4,244 children and adolescents (51.6 % boys) with a total of 18,793 annual outpatient visits.

Definition of variables

Severe hypoglycemia was defined according to the ISPAD 2014 guidelines as a hypoglycemic episode leading to loss of consciousness and/or seizures requiring parental assistance[13]. Severe hypoglycemia was registered yearly as a numeric variable.

HbA1c was measured annually at the central national Diabetes Control and Complications Trial (DCCT) standardized laboratory at Herlev Hospital, Copenhagen, using a high-pressure liquid chromatographic method (Tosoh Bioscience, South San Francisco, CA, USA). The HbA1c values were validated twice monthly by the European Reference Laboratory and aligned with DCCT values. HbA1c values were reported according to the International Federation of Clinical Chemistry standard (IFCC) in mmol/mol. The reported SH associated absolute changes in HbA1c are reported in both IFCC (mmol/mol) and National Glycohemoglobin Standardization Program (NSGP) (%) units.

Statistics

Descriptive characteristics are reported as mean (standard deviation) or percentage of total. When data are aggregated across all recorded visits, such that most patients contribute with more than one visit, only means or percentages are provided (Table 1). Skewed data distributions are presented as medians and interquartile ranges (Q1;Q3). A p-value of < 0.05 was considered statistically significant.

Data were analyzed using a mixed-effects model with log-transformed HbA1c as outcome and a random intercept for patients and a random effect of diabetes duration. The cumulative number of severe hypoglycemic events (0, 1, 2, 3, 4, >4 events) and time since last SH episode (1: since last visit, 2: between two previous visits, 3: more than two visits ago) were included as explanatory variables. “Time since last SH episode” allows us to test whether the effect of an SH episode is immediate or evolves over time. The ‘combined effect’ covers that there is a significant immediate effect and in addition to that a significant effect of time. The primary analyses were adjusted for age (≤6, 6-12, >12 years), gender and diabetes duration (years, modeled with a natural spline). This model was used to predict the expected mean HbA1c for given values of covariates.

Additional analyses were adjusted for treatment modality (1: MDI with human insulin, 2: MDI with insulin analogs, 3: insulin pump (analogs)) and frequency of SMBG (1: ≤ 2, 2: 3-5, 3: 6-9, 4: >10 times / day), 5: continuous glucose monitoring (CGM)).

Participants diagnosed with T1D prior to 2008 were included in the study with the available history of SH. Participants lacking information on previous SH were included as having had no prior episodes of SH (n=278). A sensitivity analysis was performed assuming one previous episode of SH; this did not alter the impact of SH on the reported HbA1c.

Results

At T1D onset, the mean age (SD) was 9.0 (4.1) years. At inclusion in the study, median diabetes duration (Q1;Q3) was 1.2 (0.9; 3.0) years; 92.3% of the included were of Danish ethnicity. The median follow-up time was 2.9 (1.0;5.1) years and the median diabetes duration at last visit was 5.0 (2.7;8.1) years. A total of 506 patients experienced one or more episode of SH; 294 patients had one episode, 115 patients had two episodes, 55 patients had three episodes, 15 patients had four episodes and 27 patients had more than four episodes of SH during the observation period. Characteristics of the participants stratified by number of previous SH episodes are shown in Table 1. In total, the 4,244 participants had 18,793 outpatient visits. Use of insulin pump was the most common treatment modality across all SH groups. Neither the treatment modalities in the four SH groups, nor frequency of SMBG or CGM use were statistically different in the four SH groups.

Effect of SH episodes: Episodes of SH were associated with a progressively increasing HbA1c at first outpatient visit 0-12 months post SH (Table 2). When adjusting for age, gender and diabetes duration; the HbA1c in patients with one SH episode was 1.1% (CI= (0.0;2.6, p=0.02)) higher than in patients with no previous episodes. For patients with two SH episodes, the estimated increase was 3.3% (CI=1.3;5.6, p<0.01). For an average HbA1c of 64 mmol/mol (HbA1c (NSGP) of 8%) this SH-associated change represents an increase in HbA1c in the range of 2.1 mmol/mol (IFCC)(CI:0,05;3.6 mmol/mol) corresponding to approximately 0.26% (NGSP).

Effect of time: At the following visits, the trajectory of HbA1c showed a characteristic pattern, as illustrated in figure 1 which shows the predicted six-year trajectories in HbA1c for three hypothetical patients with diabetes onset at the age of 6 years, who only differ with respect to the occurrence of SH. Patient 1: No SH episodes; Patient 2: 1 SH episode in year 2; Patient 3: 2 SH episodes in year 1 and 4. In addition to the immediate adverse effect of experiencing an SH (1.1% at the first outpatient visit after the first SH, Figure 1, Patient 1 vs Patient 2), no significant further worsening of glycemic control was seen between visits 1 and 2 (12-24 months post SH) (0.8% (CI= (-0.5%, 2.0%), p=0.24), but at visit 3 (24-36 months post SH), HbA1c levels were significantly higher, about 2% (CI= (0.7%, 3.4%), p=0.003). This time-dependent worsening of glycemic control followed the first episode of SH only. Thus, there was no evidence of an additional time-dependent increase after later events.

The combined effects of immediate worsening after SH episodes and further increase in HbA1c with time since first SH translates into an accumulated and lasting increase in HbA1c of e.g. ~5% for patients with two SH episodes or more. For an average HbA1c of 64 mmol/mol (HbA1c (NSGP) of 8%) this change represents an increase in HbA1c in the range of 3.2 mmol/mol (IFCC) corresponding to approximately 0.4% (NGSP).

Adjusting for treatment modality and frequency of SMBG or CGM use did not change the association between SH and HbA1c, but effect sizes were slightly attenuated (results not shown).

Discussion

This population-based register study among Danish children and adolescents with T1DM is the first to describe the trajectory of glycemic control following episodes of SH. We observed that SH episodes were followed by progressive glycemic deterioration; thus, multiple episodes were associated with a further increase in HbA1c. Additionally, we noticed that the glycemic deterioration following the first episode of SH worsened over time. At the third visit (24-36 months) after the first episode, HbA1c had increased with approximately 2% on top of the immediate impact of the episode. The accumulated and lasting deterioration in glycemic control for patients with two SH episodes or more was approximately 5%, equivalent to a rise in HbA1c of 3-4 mmol/mol depending on the initial level. This change is clinically relevant due to the increased risk of later complications, as data from the DCCT study revealed that a reduction in HbA1c of about 3 mmol/mol reduced the progression of diabetic retinopathy[14].

Over the past decade, diabetes treatment technology has moved from injection therapy with human insulin (neutral protamine Hagedorn (NPH)) towards frequent use of insulin analogs (Detemir and Glargine) and/or insulin pumps, and from few SMBG to more frequent SMBG or CGM. Some studies have reported a positive impact of insulin analogs,[15,16] insulin pumps[3,5,6,17] and frequent glucose monitoring[6] on the risk of SH; others have failed to confirm the positive effect of insulin analogs[18] and insulin pumps[19] on the SH risk. We observed that several patients with SH changed treatment modality from insulin pen to insulin pump. However, in accordance with other studies[20], we observed a general trend among children and adolescents towards treatment with insulin analogs and/or insulin pumps during the study period[12]. Supplementary analyses were performed to adjust our findings for a potential effect of treatment modality and frequency of SMBG or CGM. These adjustments did not significantly change the overall interpretation of SH as a risk factor for glycemic deterioration.

CGM use was low in the present study compared to clinical pediatric practice of today in Denmark. Studies have reported reduced fear of hypoglycemia[21] and improved glycemic control in children and adolescents using CGM[22]. Future studies are needed to investigate if CGM use may also prevent the deteriorating effect of SH on glycemic control reported in the present study.

The SH-associated glycemic deterioration may in part reflect a change in emotional distress and/or avoidance behavior among the children/adolescents and/or their parents. Studies have reported that episodes of mild hypoglycemia as well as SH is a predictor of fear of hypoglycemia (FOH) in both children/adolescents and their parents[23]. FOH causes psychological stress and may affect quality of

life in the patients as well as their parents[24]. Accordingly, a number of studies have reported that FOH is associated with changes in diabetes regulatory behavior with either increased number of glucose measurements[25] or avoidance behavior towards maintenance of an elevated blood glucose level among children[8] and adolescents[23]. However, the relationship between FOH and glycemic control in cross sectional studies may not be straightforward[26] as only some[8,27] but not all[28] studies report a positive association between FOH and HbA1c, indicating that many factors play a role in overall glycemic control. Conversely, the deterioration in glycemic control after SH could be due to a general poorer diabetes self-care in the groups with one or more SH episodes. However, we did not find differences in SMBG or CGM in these groups compared with the group without SH.

A subgroup of children and adolescents may be genetically[29] or physiologically predisposed to an increased risk of SH[30]. Diminished counter regulatory response has been shown early after diabetes diagnosis[31], differences in counter regulatory response between patients have been described[32], and a variant in the β-2 receptor gene has been shown to be associated with SH[29]. It is therefore possible that risk of SH and subsequent dysregulation belongs to a yet unrecognized genotype predisposing to hypoglycemia as well as dysregulation. However, further studies are needed to elucidate this.

Strengths and limitations. The national population-based design with a high data completeness and a clear definition of SH is a strength of the present study. However, the DanDiabKids provides only annual data on SH and HbA1c, and exact dates of SH episodes are thus not available. It would have been optimal to model the trajectory of glycemic control in immediate association with the episodes of SH. Nevertheless, the data and the population-based design with a large sample size provide solid evidence of a long-term and persisting effect of SH on glycemic control, which is likely to also apply to children and adolescents with T1D in other countries. It is a weakness of the present study that we do not have data assessing minor hypoglycemia as they may also impact on diabetes behavior and glycemic control. It would also be of interest to investigate the impact of SH on glycemic control applying the expanded ISPAD 2018 guidelines not requiring coma or convulsions but only severe cognitive impairment and need for external assistance[33]. Nevertheless, we find that HbA1c remained elevated for years after an SH episode indicating that the assumed psychological and/or behavioral burden, may not be of a transitory but rather of lasting concern.

In conclusion, we have revealed a progressive increase in HbA1c after episodes of SH in children and adolescents with T1D. Thus, an acute complication such as SH may translate into increased risk of long-term complications if not addressed appropriately. Hopefully, the rapid development of improved diabetes treatment technologies including closed-loop systems will reduce the incidence of SH further. Nevertheless, special attention to fear of hypoglycemia after an episode of SH should be a central and standard part of the routine diabetes outpatient management of children and adolescents with T1D.

References

1. DiMeglio LA, Acerini CL, Codner E, et al. ISPAD clinical practice consensus guidelines 2018: Glycemic control targets and glucose monitoring for children, adolescents, and young adults with diabetes. *Pediatr Diabetes*. 2018;19 Suppl 27:105-114.

2. Hypoglycemia in the diabetes control and complications trial. the diabetes control and complications trial research group. *Diabetes*. 1997;46(2):271-286.

3. Karges B, Schwandt A, Heidtmann B, et al. Association of insulin pump therapy vs insulin injection therapy with severe hypoglycemia, ketoacidosis, and glycemic control among children, adolescents, and young adults with type 1 diabetes. *JAMA*. 2017;318(14):1358-1366.

4. Haynes A, Hermann JM, Miller KM, et al. Severe hypoglycemia rates are not associated with HbA1c: A cross-sectional analysis of 3 contemporary pediatric diabetes registry databases. *Pediatr Diabetes*. 2017;18(7):643-650.

5. Birkebaek NH, Drivvoll AK, Aakeson K, et al. Incidence of severe hypoglycemia in children with type 1 diabetes in the nordic countries in the period 2008-2012: Association with hemoglobin A 1c and treatment modality. *BMJ Open Diabetes Res Care*. 2017;5(1):e000377.

6. Fredheim S, Johansen A, Thorsen SU, et al. Nationwide reduction in the frequency of severe hypoglycemia by half. *Acta Diabetol*. 2015;52(3):591-599.

7. Johnson SR, Cooper MN, Davis EA, Jones TW. Hypoglycaemia, fear of hypoglycaemia and quality of life in children with type 1 diabetes and their parents. *Diabet Med*. 2013;30(9):1126-1131.

8. Freckleton E, Sharpe L, Mullan B. The relationship between maternal fear of hypoglycaemia and adherence in children with type-1 diabetes. *Int J Behav Med*. 2014;21(5):804-810.

9. Michaud I, Henderson M, Legault L, Mathieu ME. Physical activity and sedentary behavior levels in children and adolescents with type 1 diabetes using insulin pump or injection therapy - the importance of parental activity profile. *J Diabetes Complications*. 2017;31(2):381-386.

10. Svensson J, Cerqueira C, Kjaersgaard P, et al. Danish registry of childhood and adolescent diabetes. *Clin Epidemiol*. 2016;8:679-683.

11. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. part 1: Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med*. 1998;15(7):539-553.

12. Sildorf SM, Hertel NT, Thomsen J, et al. Treatment intensification without improved HbA1c levels in children and adolescents with type 1 diabetes mellitus. *Diabet Med*. 2016;33(4):515-522.

13. Ly TT, Maahs DM, Rewers A, et al. ISPAD clinical practice consensus guidelines 2014. assessment and management of hypoglycemia in children and adolescents with diabetes. *Pediatr Diabetes*. 2014;15 Suppl 20:180-192.

14. Lind M, Oden A, Fahlen M, Eliasson B. The shape of the metabolic memory of HbA1c: Re-analysing the DCCT with respect to time-dependent effects. *Diabetologia*. 2010;53(6):1093-1098.

15. Ferguson SC, Strachan MW, Janes JM, Frier BM. Severe hypoglycaemia in patients with type 1 diabetes and impaired awareness of hypoglycaemia: A comparative study of insulin lispro and regular human insulin. *Diabetes Metab Res Rev*. 2001;17(4):285-291.

16. Holleman F, Schmitt H, Rottiers R, Rees A, Symanowski S, Anderson JH. Reduced frequency of severe hypoglycemia and coma in well-controlled IDDM patients treated with insulin lispro. the benelux-UK insulin lispro study group. *Diabetes Care*. 1997;20(12):1827-1832.

17. Jakisch BI, Wagner VM, Heidtmann B, et al. Comparison of continuous subcutaneous insulin infusion (CSII) and multiple daily injections (MDI) in paediatric type 1 diabetes: A multicentre matched-pair cohort analysis over 3 years. *Diabet Med*. 2008;25(1):80-85.

18. Tamas G, Marre M, Astorga R, et al. Glycaemic control in type 1 diabetic patients using optimised insulin aspart or human insulin in a randomised multinational study. *Diabetes Res Clin Pract*. 2001;54(2):105-114.

19. Blackman SM, Raghinaru D, Adi S, et al. Insulin pump use in young children in the T1D exchange clinic registry is associated with lower hemoglobin A1c levels than injection therapy. *Pediatr Diabetes*. 2014;15(8):564-572.

20. Foster NC, Beck RW, Miller KM, et al. State of type 1 diabetes management and outcomes from the T1D exchange in 2016-2018. *Diabetes Technol Ther*. 2019;21(2):66-72.

21. Ng SM, Moore HS, Clemente MF, Pintus D, Soni A. Continuous glucose monitoring in children with type 1 diabetes improves well-being, alleviates worry and fear of hypoglycemia. *Diabetes Technol Ther*. 2019;21(3):133-137.

22. Al Hayek AA, Robert AA, Al Dawish MA. Evaluation of FreeStyle libre flash glucose monitoring system on glycemic control, health-related quality of life, and fear of hypoglycemia in patients with type 1 diabetes. *Clin Med Insights Endocrinol Diabetes*. 2017;10:1179551417746957.

23. Gonder-Frederick LA, Fisher CD, Ritterband LM, et al. Predictors of fear of hypoglycemia in adolescents with type 1 diabetes and their parents. *Pediatr Diabetes*. 2006;7(4):215-222.

24. Stahl-Pehe A, Strassburger K, Castillo K, et al. Quality of life in intensively treated youths with early-onset type 1 diabetes: A population-based survey. *Pediatr Diabetes*. 2014;15(6):436-443.

25. Wild D, von Maltzahn R, Brohan E, Christensen T, Clauson P, Gonder-Frederick L. A critical review of the literature on fear of hypoglycemia in diabetes: Implications for diabetes management and patient education. *Patient Educ Couns*. 2007;68(1):10-15.

26. Gonder-Frederick L, Nyer M, Shepard JA, Vajda K, Clarke W. Assessing fear of hypoglycemia in children with type 1 diabetes and their parents. *Diabetes Manag (Lond)*. 2011;1(6):627-639.

27. Haugstvedt A, Wentzel-Larsen T, Graue M, Sovik O, Rokne B. Fear of hypoglycaemia in mothers and fathers of children with type 1 diabetes is associated with poor glycaemic control and parental emotional distress: A population-based study. *Diabet Med*. 2010;27(1):72-78.

28. Amiri F, Vafa M, Gonder-Frederick L. Glycemic control, self-efficacy and fear of hypoglycemia among iranian children with type 1 diabetes. *Can J Diabetes*. 2015;39(4):302-307.

29. Rokamp KZ, Olsen NV, Faerch L, Kristensen PL, Thorsteinsson B, Pedersen-Bjergaard U. Impact of genetic polymorphism in the beta2-receptor gene on risk of severe hypoglycemia in patients with type 1 diabetes. *J Clin Endocrinol Metab*. 2018;103(8):2901-2908.

30. Pacaud D, Hermann JM, Karges B, et al. Risk of recurrent severe hypoglycemia remains associated with a past history of severe hypoglycemia up to 4 years: Results from a large prospective contemporary pediatric cohort of the DPV initiative. *Pediatr Diabetes*. 2018;19(3):493-500.

31. Siafarikas A, Johnston RJ, Bulsara MK, O'Leary P, Jones TW, Davis EA. Early loss of the glucagon response to hypoglycemia in adolescents with type 1 diabetes. *Diabetes Care*. 2012;35(8):1757-1762.

32. Adamson U, Lins PE, Efendic S, Hamberger B, Wajngot A. Impaired counter regulation of hypoglycemia in a group of insulin-dependent diabetics with recurrent episodes of severe hypoglycemia. *Acta Med Scand*. 1984;216(2):215-222.

33. Abraham MB, Jones TW, Naranjo D, et al. ISPAD clinical practice consensus guidelines 2018: Assessment and management of hypoglycemia in children and adolescents with diabetes. *Pediatr Diabetes*. 2018;19 Suppl 27:178-192.

Table 1

Number of severe hypoglycemia episodes	0	1	2	≥ 3
Number of visits	15543	1676	800	774
Sex (% male)	50	52	47	55
BMI-SDS	0.72	0.85	0.77	0.89
HbA1c (mmol/mol)	63.4	67.6	71.1	70.4
Treatment				
Human insulin (%)	9.0	8.3	6.8	6.9
Insulin analog (%)	27.4	28.9	36.0	29.1
Insulin pump (%)	63.6	62.8	57.2	64.1
Self-monitored blood glucose				
≤2 day (%)	5.3	5.1	6.5	5.8
3-5 day (%)	34.4	42.6	48.0	43.2
6-9 day (%)	40.9	38.4	35.8	39.8
>10 day (%)	13.3	9.8	7.8	5.4
Continuous glucose monitoring (%)	6.1	4.0	2.0	5.9

Table 1. Participant characteristics at annual visits stratified by number of previous episodes of severe hypoglycemia (SH). SDS, standard deviation score. BMI-SDS and HbA1c (mean).

Table 2

SH	n	Estimate (%)	CI	P-value
1	294	1.1	0.0 - 2.6	0.02
2	115	3.3	1.3 - 5.6	<0.01
3	55	1.8	-1.0 - 4.7	0.14
4	15	5.9	1.7 - 10.3	<0.01
>4	27	5.2	1.0 - 9.7	0.01

Table 2. Percentage increase in HbA1c following episodes of severe hypoglycemia (SH) compared with no previous SH episodes

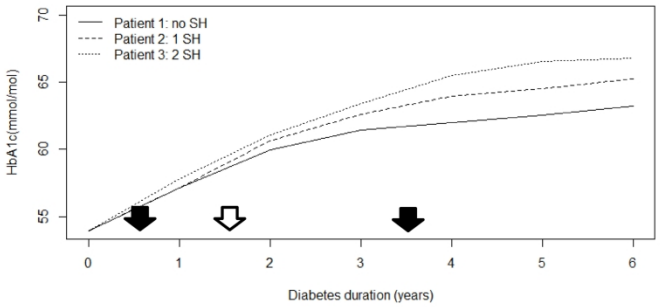

Figure 1: Predicted mean six-year trajectories for three hypothetical groups of patients with diabetes onset at six years age, who only differ with respect to the occurrence of SH. Prediction adjusted for age (6-12 years), gender (female) and duration of diabetes.
Patient 1: No SH; Patient 2: 1 SH in 2nd year (open arrow); Patient 3: 2 SH in 1st and 4th year (filled arrows).

209x296mm (300 x 300 DPI)